

**GROWTH HORMONE LEVELS IN
NEWBORNS IN RELATION TO
GESTATIONAL AGE
AND
ANTHROPOMETRIC INDICES**

THESIS

FOR

**DOCTOR OF MEDICINE
(PEDIATRICS)**



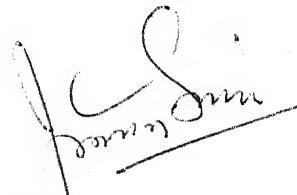
**BUNDELKHAND UNIVERSITY
JHANSI (U.P.)**

CERTIFICATE

This is to certify that the work entitled "***Growth hormone levels in newborns in relation to gestational age and anthropometric indices***" has been carried out by ***Dr. Ruchin Agarwal*** in the Department of Pediatrics, M.L.B. Medical College, Jhansi.

He has put in the necessary stay in the Department as per University regulations, and has fulfilled the conditions required for the submission of thesis according to University regulations.

Dated: 27/10/04



Dr.(Mrs.) Sheela Longia

M.D.,

Professor & Head,

Department of Pediatrics,

M.L.B. Medical College,

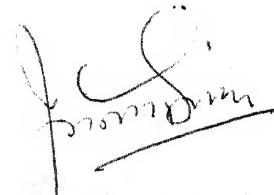
Jhansi.

CERTIFICATE

This is to certify that the work entitled "**Growth hormone levels in newborns in relation to gestational age and anthropometric indices**" which is being submitted as a thesis for M.D. (Pediatrics) Examination 2005 of Bundelkhand University, Jhansi, has been carried out by **Dr. Ruchin Agarwal** under my direct supervision and guidance.

The techniques embodied in the thesis were undertaken by the candidate himself and the observations recorded have been checked and verified by me from time to time.

Dated: 27/10/04



Dr.(Mrs.) Sheela Longia

M.D.,

**Professor & Head,
Department of Pediatrics,
M.L.B. Medical College,**

Jhansi.

(Guide)

CERTIFICATE

This is to certify that the work entitled "***Growth hormone levels in newborns in relation to gestational age and anthropometric indices***" which is being submitted as a thesis for M.D. (Pediatrics) Examination 2005 of Bundelkhand University, Jhansi, has been carried out by **Dr. Ruchin Agarwal** under my direct supervision and guidance.

The techniques embodied in the thesis were undertaken by the candidate himself and the observations recorded have been checked and verified by me from time to time.

Dated: 27/10/04

Dr. R. K. Agarwal

M.D.,

Professor & Head,
Department of Microbiology,

M.L.B. Medical College,
Jhansi.

(Co-Guide)

CERTIFICATE

This is to certify that the work entitled "***Growth hormone levels in newborns in relation to gestational age and anthropometric indices***" which is being submitted as a thesis for M.D. (Pediatrics) Examination 2005 of Bundelkhand University, Jhansi, has been carried out by ***Dr. Ruchin Agarwal*** under my direct supervision and guidance.

The techniques embodied in the thesis were undertaken by the candidate himself and the observations recorded have been checked and verified by me from time to time.

Dated: / /

Dr. (Mrs.) Mridula Kapoor

M.S.,

Professor & Head,

Department of Obstetrics and Gynaecology,

M.L.B. Medical College,

Jhansi.

(Co-Guide)

Acknowledgement

Acknowledgement of the favours received and privileges enjoyed is not simply a matter of going through time honoured ritual. It is having the pleasure and satisfaction of discharging various debts of gratitude. I am sure I can never manage to bring forth my sincere gratitude to all who have meant so much in successful completion of this project, yet I shall try my best to do so.

It is with a profound sense of gratitude, that I pay my obeisance to my esteemed and learned teacher and Guide Dr. (Mrs.) Sheela Longia M.D., Professor & Head, Department of Pediatrics, M.L.B. Medical College, Jhansi, for whom my reverence has always been at its zenith. Her motherly attitude, valuable suggestions, exemplary dedication and constructive criticism have gone a long way towards the success of this work.

Words fail to express my deepest sense of gratitude to my Co-Guide Dr. R. K. Agarwal M.D., Professor & Head, Department of Microbiology, M.L.B. Medical College, Jhansi, who with his unfathomed knowledge and untiring zest for work guided me unflinchingly throughout this humble venture.

In no less degree I owe my sincere most thank to my Co-Guide Dr. (Mrs.) Mridula Kapoor M.S., Professor & Head, Department of Obstetrics and Gynaecology, M.L.B. Medical College, Jhansi, whose firm initiative, timely and constructive criticism, divine inspiration held me finish this uphill task.

I find myself indebted to Dr. Anil Kaushik, M.D, Associate Professor, Department of Pediatrics, M.L.B. Medical College, Jhansi, for

giving me requisite guidance, inspiration and encouragement to take up and complete such an enormous job.

I also extend my deepest regards to Dr. R.S. Sethi, M.D., D.C.H. Associate Professor, Department of Pediatrics, M.L.B. Medical College, Jhansi. He had always been ready with invaluable suggestions and unending encouragement. It will not be an exaggeration to say that he has been instrumental in the completion of my work.

I am highly thankful to Dr. Lalit Kumar, M.D., D.C.H., Assistant Professor, Department of Pediatrics, M.L.B. Medical College, Jhansi, who has been a constant source of inspiration in my tough times.

I bow in reference to those infants who have formed the material for this study, with a hope to contribute a drop in the ocean of present knowledge, which in days to come would unchain them from the bonds of agony.

Although friends perhaps do not need these words, but I would fail in my duty by not giving thanks I am especially thankful to Dr. Om Shankar Chaurasiya, Dr. Vivek Johari and Dr. Rajeev Gupta, who left no stone unturned to help me fulfilling this work.

At this moment of glory and award, I accept that all credit goes to my parents, my family, whose affection, patience and sacrifice have made all this come true. I can't express my feelings in words towards my brother Dr. Sachin Agarwal, whose constant guidance has sailed me through thicks and thins of life.

At last, but not the least, I am also thankful to Mr. Praveen Arora (Crux Computers), who worked with me day and night to help me finish this job in time.

Date: 27/10/04

Ruchin Agarwal
Ruchin Agarwal

Contents

CONTENTS

Sl. No.	Description	Page No.
1.	<i>Introduction</i>	1.....5
2.	<i>Aims and objectives</i>	6.....6
3.	<i>Review of Literature</i>	7.....31
4.	<i>Material and Methods</i>	32.....40
5.	<i>Observations</i>	41.....51
6.	<i>Discussion</i>	52.....61
7.	<i>Summary</i>	62.....66
8.	<i>Conclusion</i>	67.....68
9.	<i>Bibliography</i>	69.....83
10.	<i>Working Proforma</i>	

Introduction

Introduction

Growth hormone (HGH, Somatotropin) is a polypeptide hormone secreted by pituitary gland, which is located within the sella turcica ventral to the diaphragma sellae.

Pituitary gland comprises anatomically and functionally distinct anterior and posterior lobes. Blood supply of pituitary is derived from the superior and inferior hypophyseal arteries.

The endocrine environment of the fetus is unique with regard to the endocrine organs, the presence of certain hormones, changing and often high circulating concentrations of hormones, hormone metabolism and specialized response related to in-utero development. Although the pattern of fetal growth and development is not generally dependent on hormones with some important exceptions, the timing of these events is modulated by the level of endogenous hormones and exposure to hormone treatment. (Phillip L. Ballard, 1998).

The placenta also produces most, if not all of the releasing hormones synthesized by hypothalamus. Thus, the placenta

contributes to the circulating pool of pituitary and hypothalamic hormones in the fetus.

In general most endocrine systems of the fetus are functional by the end of the first trimester, although circulating levels of many hormones increase substantially only during the third trimester. In contrast the level of growth hormone increases during the first two-third of pregnancy and then declines towards term.

Cells that produce growth hormone, ACTH are detectable at 9th week of gestation. Hormone producing cells can differentiate and hormone synthesis in the absence of hypothalamic stimulation has been documented in embryonic pituitary in several in vivo studies.

During the second and third trimesters of pregnancy the variant form becomes the predominant form of growth hormone in maternal circulation and the pituitary form decreases. The proportion of growth hormone variants in circulation are similar to those in the pituitary except that the 20Kda form and the oligomeric forms are more prominent in the circulation, because of their slower metabolic clearance. (Michael O. Thorner et al).

Growth hormone is not the principle direct stimulator of growth, but it acts mainly by stimulating the formation of other hormones known as somatomedins or IGF1 and IGF2.

IGF1 or somatomedin -c, the more important factor for postnatal growth is produced in liver. IGF2 is much less affected by growth hormone and has a role in growth of fetus before birth. In contrast to other hormones, the IGFs' do not arise from a single organ source but are secreted by most tissues in response to growth hormone stimulation and circulate in plasma bound to high affinity binding proteins. Animal studies suggest that liver is the greatest single source of total serum IGF activity.

There is an indirect evidence that the somatomedin group of peptides may be involved in human fetal development. For example, levels of somatomedins in cord plasma show a positive correlation with birth weight or length.

Levels of IGF1, IGF2 are low throughout gestation with only a small increase in IGF1 prior to 32 – 34 weeks. From then, until term there is two to fourfold rise in both peptides, although level at birth are lower than in normal adults. IGF1 level is low at birth and rises

gradually throughout childhood to reach adult level at 8 – 10 years age (I.K. Asthan, J. Zapf et al).

This lead to Daughaday's original hypothesis that growth promoting effect of growth hormone were mediated by stimulation of liver to secrete the IGFs' which in turn were carried peripherally to exert their effect on cartilage and extra skeletal cell proliferation. More recent evidence favours an autocrine role or a paracrine role rather than classic endocrine concept. IGF levels increase in extra-hepatic tissue in response to growth hormone stimulation, reaching a peak before maximum blood levels occur. IGF probably exerts its effect locally within these tissues before reaching the circulation, where it is complexed with binding proteins, which may restrict or modulate further activity, before clearance from the circulation.

There are two theories of growth hormone action. The growth hormone hypothesis and the somatomedin hypothesis.

According to somatomedin hypothesis the anabolic actions are mediated by IGF. Some effects of growth hormones are independent of IGF activity, such as enhancement of lipolysis, stimulation of amino-acid transport in diaphragm and enhancement of protein synthesis.

Specific receptor for IGF have been identified. "Type 1" receptor is similar to insulin receptor and binds preferentially IGF1, but also binds IGF2 and insulin with lower affinity.

Type 2 receptor is different, it binds IGF2 preferentially, IGF1 with low affinity and does not bind insulin. IGF1 is predominantly responsible for the growth promoting effect of growth hormones, whereas, IGF2 may mediate other metabolic actions of growth hormones. Growth hormone is detectable in fetal serum at the end of first trimester and its concentration rises rapidly to reach a peak of 100 – 150 ngm / L at about 20 week of gestation (Gluckman et al, 1981). Mean levels decrease to about 30 ngm / L in cord serum at term and continue to fall during the early postnatal months. (Michael O. Thorner).

Although growth hormone is not necessary for somatic growth in first six months of life but its alteration in perinatal asphyxia, abnormal mode of delivery, degree of apgar score, prematurity, congenital central nervous system infection have been reported in the recent past, which may affect the somatic growth of neonate later on.

Aims

&

Objectives

Aims and objectives

1. To measure the growth hormone levels in full-term and pre-term neonates.
2. To study the relationship of gestational age, sex, birth weight, length and head circumference with growth hormone levels in neonates.

Review Of Literature

Review of Literature

Growth hormone is the most abundant anterior pituitary hormone. It is a 191 amino acid polypeptide hormone secreted by anterior pituitary.

Pituitary gland comprises anatomically and functionally distinct anterior and posterior lobes. Blood supply of pituitary is derived from the superior and inferior hypophyseal arteries.

The pituitary is derived from two sources, epithelial and neural portion. The epithelial portion includes pars distalis, intermediate lobe and pars tuberalis. It originates from evagination of Rathke's pouch. The neural portion, which includes the infundibulum, neural stalk and posterior lobe, arises in the saccus infundibulum in diencephalon. The human fetal pituitary can synthesize and secrete HGH by 8 – 10 weeks of gestation (Delbert A. Fisher). Acidophilic cells are detectable at about third month of gestation, basophilic cells somewhat latter. Cells that produce GH, ACTH are detectable at ninth week of gestation (Michael. O Thorner et al).

Growth hormone is secreted by somatotropes which are acidophilic cells lying in the anterior lobe of the pituitary. Somatotropes make about 50% of the anterior pituitary cells.

HGH gene is located on long arm of chromosome 17. Its gene (HGH1) is first in the cluster of 5 closely related genes (q 22 – 24). The four other genes have more than 90% sequence identity with the GH1 gene. They consist of CS1 and CS2 genes, which encode the same HCS (Human Chorionic Somatomammotropin), a placental growth hormone (GH2) and a pseudogene (CSP).

Syntiotrophoblast of placenta produce large quantities of HCS and placental growth hormone replaces pituitary growth hormone in maternal circulation after 20 weeks of gestation. When the fetal gene lacks CS1, CS2 and CSP genes – the HCS and GH are absent but fetal growth and post partum lactation are normal (John S. Parks).

Growth hormone secretion is controlled by dual hypothalamic regulation. Release of growth hormone is stimulated by GHRH also known as somatocrinin, by regulating the transcription of growth hormone m-RNA by controlling cyclic AMP levels (Baringa et al, 1983).

Growth hormone secretion is inhibited by growth hormone release inhibiting hormone, also known as somatostatin. It appears to determine the timing and amplitude of growth hormone pulse, but has no effect on growth hormone synthesis. Somatostatin is produced by periventricular and medial preoptic area of anterior hypothalamus (Alpert, 1957, Halasz 1994).

A second stimulator system, parallel to that involving HGRH receptor is activated by Gherlin. Gherlin is produced in arcuate nucleus of hypothalamus and in much greater quantities by stomach. Fasting stimulates and feeding inhibits Gherlin release into circulation. (John S. Parks)

The pattern of growth hormone secretion depends upon a number of factors, including stage of development, nutritional state, sleep stage, stress (Traumatic, Surgical, Inflammatory), exercise and various neurogenic metabolic and hormonal factors.

The stimulus for secretion is releasing factor or neural signal that induces rapid changes in intracellular calcium concentration leading to fusion of granules with plasma membrane and its release into extracellular environment.

Peaks of growth hormone secretion occur when peaks of GHRH coincide with troughs of somatostatin with the highest peak occurring during sleep

After protein processing, peptide hormones are stored in secretory granules which are poised beneath the plasma membrane for immediate release into the circulation.

The secretion of growth hormone is pulsatile, which increases after meals, exercise and during slow wave sleep. It is inhibited during REM sleep. Growth hormone secretion is inhibited by cortisol, free fatty acids and medroxyprogesterone. Growth hormone is necessary for normal linear growth. Its deficiency causes short stature and excess leads to gigantism. Growth hormone does not appear to be the principle direct stimulator of growth but it acts indirectly by formation of other hormones. These factors, known as somatomedins or IGF, are dependent and are responsible for growth stimulation (Yamashita et al, 1986). IGF1 or somatomedin – c, the most important somatomedin for postnatal growth is produced in liver, chondrocytes, kidney, muscle, pituitary and gastrointestinal tract. Liver is the main source.

IGF1 circulate in plasma in bound form with 6 distinct binding proteins. The net effect of binding is to increase the $t_{1/2}$ of IGF1 to 3 to 18 hours, as compared with the $t_{1/2}$ of 20 – 30 minutes for unbound hormones.

GH is bound in plasma to proteins that is a large fragment of the extracellular domain of growth hormone receptor. Its concentration is an index of number of growth hormone receptors in tissues.

GH is metabolized rapidly at least partly in the liver. The $t_{1/2}$ of circulating growth hormone is 6 to 20 minutes. Growth hormone receptor is a 620 amino acid protein with a large extracellular domain, a transmembrane domain and a large cytoplasm portion. Growth hormone has two binding sites for receptors. Hormones binding to receptors produces as homodimer. Dimerization is essential for growth hormone action.

The prolactin and growth hormone receptors are part of cytokines receptors super family. These receptors signal through activation of JAK family of intracellular tyrosine kinases and the STAT family of transcription factors. Growth hormone activates JAK 2 (and to a less extent JAK1 and 3), and STAT 1 , 3 and 5. The

specificity of the activation of JAK-STAT pathway depends on the cell type (Delbert A Fisher).

Though growth hormone exerts direct effects in target tissues, many of its physiological effects are mediated indirectly through IGF1, a potent growth and differentiation factor. The major source of circulating IGF1 is hepatic in origin. Peripheral tissue IGF1 exerts local paracrine actions that appear to be both dependent and independent of growth hormone. Thus, growth hormone administration induces circulating IGF1 level as well as stimulating IGF1 expression in multiple tissues.

Both IGF1 and IGF2 are bound to one of the six high affinity circulating IGF binding proteins (IGFBPs), that regulate IGF bioactivity. Levels of IGFBP3 are growth hormone dependent, and it serves as the major carrier protein for circulating IGF1. Growth hormone deficiency and malnutrition are associated with low IGFBP3 levels. IGFBP1 and 2 regulate local tissue IGF action, but do not bind appreciable amounts of circulating IGF1.

The level of IGF1 at birth is lower than that of an adult and rises gradually during childhood to reach the adult level at 8 to 10 years of age.

Although IGF1 levels correlate with linear growth, the correlation is inexact, therefore, growth hormone may have some indirect influence on growth or may cause somatomedin generation in target tissues.

Heller (1954) and Jost (1953), suggested that fetal pituitary produces adrenocorticotropin hormone during intra-uterine life, and that the maternal pituitary hormone cannot reach the fetus transplacentally in such concentration as might replace that which apparently was being supplied by the fetal pituitary. Haemagglutination inhibition immunoassay procedure for growth hormone of Dominguez and Pearson was used in this study. Mean value of growth hormone in normal adult was 0.3 µg / dl, with a range of 0.1 – 0.6 µg/ dl. Patients with active acromegaly had value ranging from 0.6 to 11.5 µg/ dl, with a mean of 2.1 µg / dl. Growth hormone levels of umbilical arterial blood were significantly higher than those of umbilical venous blood with mean value of 1.99 µg / dl and means and SEM of difference of umbilical arterial and umbilical venous growth hormone was $+ 0.68 \pm 0.096 \mu \text{gm} / \text{dl}$ of serum, a highly significant difference ($p < 0.001$). The growth hormone level of umbilical venous blood was also higher than those of maternal

venous blood. The mean umbilical venous growth hormone value was $1.31 \mu\text{g} / \text{dl}$ of serum and mean and SEM of difference between umbilical venous and maternal venous growth hormone level was $+ 0.31 \pm 0.089 \mu\text{g} / \text{dl}$ of serum ($p < 0.01$).

There was no instance in which the growth hormone level in maternal venous blood was higher than that of umbilical venous blood, and in no instance the umbilical venous blood levels higher than the umbilical arterial blood level. These observations are consistent with active secretion of the growth hormone by the anterior pituitary gland of the fetus. High level of growth hormone in umbilical cord blood has also been reported by Greenwood et al (1964), Glick et al (1963) and by Kalkhoff et al (1964), by utilizing a radioimmunoassay.

Greenwood et al(1964), has reported similar levels of growth hormones in umbilical arterial and venous blood in two cases and Glick et al (1997), had similar findings in one case.

Kaplan and Grumback (1964) has shown that binding affinity of anti human growth hormone hemagglutinating antibodies for human placental lactogen was less than half for human growth hormone. This observation was confirmed by using a purified human

placental lactogen prepared by Dr. Henry Friesen. This preparation was assayed by hemagglutination inhibition assay for human growth hormone, 1600 times the amount of human placental lactogen was needed to produce hemagglutination inhibition than with human growth hormone. It indicate that values for maternal serum human growth hormone reported here represent human growth hormone and not human placental lactogen. Higher level of human growth hormone in the fetal circulation suggest that human growth hormone was not transferred from the mother. Preliminary studies of human placental lactogen suggest that it does not cross the placenta from mother to fetus, but the result are not conclusive because lack of sensitivity and specificity of the assays.

Kaplan et al (1972) measured the content and concentration of growth hormone in human fetal pituitary gland from 68 days of gestation to term and in the pituitary gland of one month to 9 years old children. The human pituitary gland secretes polypeptide hormones early in gestation. Acidophilic cells have been observed in the anterior hypophysis by the 9th week of gestation by histochemical method (Covell 1927 & Daikoku 1958) by electron microscopy method of Dubois P (1968) and by immunofluorescence

technique of Grumback (1962), Ellis et al (1966). Immunoassay of human growth hormone, human chorionic somatotropin and insulin were performed by double antibody method. Growth hormone was detected in the fetal pituitary gland as early as 68 days of gestation, the youngest pituitary gland assayed. At 10-14 weeks of gestation, the mean content of growth hormone was $0.44 \pm 0.20 \text{ } \mu\text{g/mg}$ pituitary and the mean concentration was $0.14 \pm 0.9 \text{ } \mu\text{g / mg}$. At 15-19 weeks mean growth hormone content was $9.21 \pm 2.31 \mu\text{g/mg}$ pituitary and mean concentration was $2.02 \pm 0.55 \text{ } \mu\text{g / mg}$ of pituitary. At 20 - 24 weeks the mean content was $59.38 \pm 11.08 \text{ } \mu\text{g}$ and mean concentration was $3.83 \pm 0.60 \text{ } \mu\text{g / mg}$, at 25 - 29 weeks mean content was $225.93 \pm 40.49 \text{ } \mu\text{g}$ and mean concentration $9.24 \pm 3.25 \text{ } \mu\text{g / mg}$; at 30 – 34 weeks with the mean content was $577.67 \pm 90 \text{ } \mu\text{g}$ with mean concentration of $9.34 \pm 1.22 \text{ } \mu\text{g / mg}$, at 35 - 40 weeks the mean content was $675.17 \pm 112.33 \text{ } \mu\text{g}$ and the mean concentration was $7.5 \pm 1.47 \text{ } \mu\text{g / mg}$. The increment in the content and concentration of growth hormone bore a significant relationship to gestational age, crown-rump length, and to the weight of the pituitary gland.

They observed that the peak level of growth hormone was attained by 20 - 24 weeks of gestation. After that the concentration of serum growth hormone showed a significant negative correlation with gestational age ($p < 0.001$).

In 17 fetuses, from which matched serum and pituitary specimens were obtained, there was no significant correlation of the concentration of serum growth hormone to the pituitary content of growth hormone ($p > 0.05$). There was no significant difference between the mean concentration at 15 – 19 weeks, 20 - 24 weeks or 25 - 29 weeks. The mean concentration of serum growth hormone at 25 – 29 weeks was significantly greater than at 30 – 40 weeks ($p < 0.02$).

Regulatory mechanisms for control of growth hormone secretion may not become fully functional until infancy by which time myelination, cortical development and synchronous EEG activity are at mature stage. (Turner et al, 1971).

Cornblath et al (1964), had studied the secretion and metabolism of growth hormone in premature and fullterm infants and measured the growth hormone levels by radioimmunoassay. The mean (\pm SD) level of growth hormone in the plasma obtained from

blood taken from the umbilical vein was 66 ± 72.2 (9 – 320) ng/ml. During the first 24 hours, the mean level was 52 ± 39.3 ng/ml with a subsequent rise to 72 ± 56.3 in the next 24 hours. Although, growth hormone levels were the same in the cord blood of both male and female infants, the males had significantly higher levels of HGH during the first month of life.

Turner et al (1971) had noted that in fetus delivered by hysterectomy at 20 –24 weeks of gestation, concentration of serum growth hormone was 3 fold higher in peripheral blood (Mean 90 ± 51 ng / ml) obtained post delivery than that noted at delivery in umbilical cord blood (mean 59 ± 22 ng / ml). At term the concentration of growth hormone was lower in umbilical venous blood samples than in fetus at 20 - 24 weeks of gestation.

Aubert et al (1972) had shown that the magnitude of serum growth hormone rise 1 hour post delivery was less in fetus delivered at term than at mid gestation. The serum rise in response to acidosis or anoxia of the fetus was significantly less in full term fetus than those delivered at mid gestation, (Turner et al, 1971). This difference in the growth hormone responsiveness to stress with maturation of fetus was consistent with hypothesis of persistent

immature state or incomplete development of control mechanism for the release of GH until early infancy.

Delayed removal of growth hormone from fetal circulation could contribute to the elevated levels of serum growth hormone. The disappearance rate of exogenously administered growth hormone was comparable in the premature infant to that observed in the child and adult, (Cornblath et al, 1965). So it was seen to be unlikely that delayed disposal of growth hormone was a major factor in the elevated serum growth hormone in the fetus. Transplacental passage of growth hormone was negligible and did not contribute to elevated fetal growth hormone levels. Human placental hormone, chronic somatomammotropin (HCS) which bear many similarities, to growth hormone have limited transplacental passage as evidenced by low concentration of human chorionic somatomammotropin in umbilical venous sera, in fetal sera in contrast to maternal sera, and by limited transfer to the fetus of HCS I^{123} administered to the mother, (Grumback et al, 1968). The concentration of human chorionic somatomammotropin in the fetal sera is only 1/20th to 1/300th of that present in the maternal circulation at that gestational age. There was no relationship between the level of maternal serum

human chorionic somatomammotropin and serum human chorionic somatomammotropin in the fetus throughout the gestation. The biological activity of human and animal fetal growth hormone had been demonstrated in animal by classic bioassay method. Available evidence suggested that neither maternal nor fetal growth hormone is essential for normal fetal growth. The birth length of a pituitary fetus, anencephalic fetus, or children with idiopathic hypopituitarism is usually within the normal range, (Nanagas et al 1926) and Dunn 1966). Children born to women with isolated growth hormone deficiency or to the mothers hypophysectomized during gestation do not show evidence of growth retardation (Chez et al, 1970). The possible role of insulin as a growth factor in the fetus is not inconsistent with its known biological action. Administration of insulin to the rat fetus induces the change in length and weight as well as an increase in body content of proteins and lipids. Body weight and width of the tibial epiphysis was increased in the hypophysectomized rat treated with insulin. Elevated circulatory level of insulin in fetus as in infants of diabetic mother and in those with transposition of great vessels were associated with increased

birth weight and length. Infants with congenital diabetes tend to be of low birth weight and length.

The role of somatomedins on skeletal growth in fetus remain speculative. Indirect evidence suggest that somatomedin may affect growth. The birth length of the children with a hereditary form of dwarfism, associated with decreased plasma somatomedin activity, was significantly retarded in contrast to the normal or near normal birth length of a pituitary fetus and children with hypothalamic hypopituitarism. Hence there may be other effectors of somatomedin synthesis in the fetus. Since the absence of GH is not rate limiting in terms of fetal growth, other humoral growth factor as yet unidentified may be present in the fetus. Nerve growth factor shown to have similarities in structure and function to that of proinsulin, may be representative of other inducer substances present during fetal life which may influence the fetal development.

Sack et al (1976) studied the normal term newborn during the first 4 hrs of life and measured serum thyrotropin (TSH), prolactin (PRL) and growth hormone level. Cord blood was collected from normal newborn at term within four days of life. The mean serum growth hormone concentration remained essentially unchanged

during the first 4 hours with mean value ranging from 24 – 42 ng / ml.

The mean serum growth hormone level did not change significantly during the first four hours of life. However in newborn there was a decrease in serum growth hormone concentration during the first 30 – 120 min. Glucose infusion tends to inhibit growth hormone release but paradoxical increase had been observed in response to glucose infusion during the neonatal life. Inhibition of growth hormone release was observed after somatostatin infusion. The fact that the growth hormone levels tend to decrease rather than increase was against the view that the thyrotropin and prolactin increments represent stress response. It also was unlikely that the transient reduction in serum growth hormone level was mediated by somatostatin, since somatostatin inhibit the thyrotropin response to thyrotropin releasing hormone. Thus hypothalamic pituitary response to parturition did not appear to represent a non specific stress response, rather selective thyrotropin releasing hormone release seems to be involved, perhaps mediated by neonatal cooling.

Nagashimha et al (1986) measured the level of growth hormone and growth hormone releasing factor in cord blood to evaluate the mechanism of high growth hormone secretion in perinatal life. Umbilical venous blood samples were obtained from normal neonates at the time of delivery. The plasma immunoreactive growth hormone releasing factor were measured by double antibody RIA method and plasma growth hormone, somatostatin (SRIF) and somatomedin-c were measured by RIA kit. The levels of plasma growth hormone, growth hormone releasing factor and somatostatin were remarkably higher than the normal range in healthy adult. The level of growth hormone (mean \pm SE) in cord blood was 23.4 ± 10.2 ng / ml as compared to 2.3 ± 0.9 ng / ml in normal adult. The levels of growth hormone releasing factor and somatostatin and somatomedin-c in cord blood were 49.5 ± 11.7 pg / ml, 41.0 ± 10.4 pg / ml and 0.22 ± 10 U/ml respectively as compared to 26.5 ± 12 pg / ml, < 15 pg / ml and 1.05 ± 0.21 U / ml in normal adult. In statistical analysis there were no relationship found among the level of growth hormone, growth hormone releasing factor and somatostatin. There were no relationship between body weight of infant, gestational age and sex and the levels of growth

hormone, growth hormone releasing factor and somatostatin. Block et al (1984) reported that neurons immunoreactive with human growth hormone releasing factor antibodies were first detected at the 29th week of gestation and suggested that first stage of differentiation and development of growth hormone producing cells in the human fetus did not depend on hypothalamic growth hormone releasing factor secretion. Shimano et al (1985) reported that the response of growth hormone secretion to human growth hormone releasing factor administration in neonate was higher than in normal children and adult. It was reported that the sensitivity of somatotropes in pituitary gland was high and that the growth hormone secretion from the hypophysis in the late stage of fetal development might already be regulated by hypothalamic growth hormone releasing factor. It was speculated that high growth hormone releasing factor secretion in addition to the high responsiveness to it might increase the secretion of growth hormone in the perinatal period and low level of somatotropin might increase the secretion of growth hormone releasing factor from the hypothalamus.

Naguib et al (1987) investigated the relationship between growth hormone, somatomedin-c non suppressible insulin like activity, weight, gestational age and 1-min apgar score in the newborn infants. Umbilical cord blood was obtained from the placental side that contained both the arterial and venous blood. Levels of growth hormone in premature, short for gestational age, appropriate age and large for gestational age neonates were 23 ± 11 ng / ml, 17.3 ± 12 ng / ml, 13.7 ± 8.5 ng / ml and 13.7 ± 12 ng / ml respectively. Levels of somatomedin-c in the same group were 0.46 ± 0.3 U / ml, 0.91 ± 0.62 U / ml, 0.82 ± 0.7 U / ml, 1.1 ± 0.8 U / ml respectively and levels of non suppressible insulin like activity were 130 ± 63 μ / ml, 220 ± 102 μ / ml, 179 ± 113 μ / ml and 214 ± 102 μ / ml respectively. It was found that growth hormone in premature infant was significantly higher than levels in large for gestational age and appropriate for gestational age infants ($p < 0.05$).

Somatomedin-c level was significantly low in premature infants compared with large for gestational age infants ($p < 0.05$) and it was significantly lower in premature group as compared to term neonates. Non suppressible insulin like activity was significantly low

in premature infants as compared with short for gestational age and large for gestational age infants ($p<0.05$) and levels were significantly low in premature as compared to term infants. There was significant negative correlation between one minute apgar score and growth hormone level in infants. There was no significant correlation between somatomedin-c or non suppressible insulin like activity and the one-minute apgar score. The higher growth hormone level in premature infants as compared to term infants supports that growth hormone may not play an important role in fetal growth.

It had been suggested that insulin might be the main hormone responsible for intrauterine fetal growth either by its direct action or by stimulation of somatomedin formation (Spencer et al, 1983,96). Somatomedin stimulate the DNA synthesis, cell multiplication and incorporation of organic sulphate into cartilage (Daughaday et al, 1976 and Zopf et al, 1986). These observations had been confirmed with pure insulin like growth factor I and II. It had been shown in vivo that insulin like growth factor was capable of stimulating growth indices and body weight in the absence of growth hormone.

It was suggested that prolactin and growth hormones are sensitive indicators of fetal and perinatal distress. Growth hormone concentrations were lower in neonates with severe hypoxic ischaemic encephalopathy than in newborn children with mild and moderate encephalopathy. It may result from a transient or sometimes even permanent damage of the hypothalamic hypophyseal axis caused by severe anoxia (Varvarigou et al, (1996), Gluckman et al (1979)).

Kapoor et al, 1996 conducted a study to measure growth hormone level in normal term and preterm neonates and to evaluate the alteration in growth hormone in birth asphyxia.

This study was carried on 64 cases of birth asphyxia including 18 preterm and 46 term and 64 neonates including 15 preterm and 50 term, matched for gestational age, sex and weight who were delivered in the hospital. Apgar scoring was done at one minute after birth and gestational age was calculated by LMP and correlated with Ballard modification of Dubowitz scoring system. Weight was recorded within one hour of birth. Neonates with gestational age less than 30 week, SGA babies and babies with congenital malformation were excluded from the study. Neonates

with apgar score less than or equal to 7 were included in study as cases and those with apgar score more than 7 were taken as control. Asphyxiated newborn were further divided into 3 groups according to their 1 minute apgar score; mild asphyxia with apgar score between 5 - 7, moderate asphyxia with apgar score 3 - 4 and severe asphyxia with apgar score 0 - 2. Two ml nonoxalate blood was taken from umbilical cord at the time of delivery in all neonates. Serum was separated in glass vial and stored at 2 - 8°C for the assay on the same day or frozen at -20°C, if the test was done later than 24 hours after collection.

Growth hormone was estimated by radio immunoassay method using code RIAK - 3 kits supplied by Radio Pharmaceuticals Division of Bhabha Atomic Research Centre, India.

The mean birth weight and gestational age of neonates included in the study was 2.59 ± 0.57 Kg (1.3-3.5 Kg) and 37.42 ± 2.5 weeks (30 - 41 weeks) respectively. Full term neonates had mean birth weight 2.99 ± 0.34 Kg (2.5 - 3.5Kg) and mean gestational 38.6 ± 1.16 weeks (37 - 41 weeks) while preterm had mean birth weight 1.92 ± 0.36 Kg (1.3 - 2.4Kg) and mean gestational age 34 ± 1.54 weeks (30 – 37 weeks).

In cord blood of term neonates ($n=50$), growth hormone concentration ranged from 15 to 30 ng/ml with a mean of 25.2 ng/ml (SD 3.8) while in preterm neonates ($n=14$) the concentration ranged from 27 to 40 ng/ml with a mean of 37.3 ng/ml (SD 4.5). The growth hormone level in cases of birth asphyxia (18 preterm and 46 term) were 40 ± 2 ng/ml in mild asphyxia, 48.5 ± 7.2 ng/ml in moderate asphyxia, 66.6 ± 24.2 ng/ml in severe asphyxia in preterm babies and 28.3 ± 2.1 ng/ml in mild asphyxia, 34.5 ± 5.4 ng/ml in moderate asphyxia and 43.8 ± 8.7 ng/ml in severe asphyxia.

There was statistically significant ($p < 0.0001$) difference among neonates in four categories, namely controls mild asphyxia, moderate asphyxia and severe asphyxia.

In this study in preterm newborns growth hormone were significantly higher in comparison to term newborns. In both preterm and term neonates growth hormone levels increased with the severity of birth asphyxia. Growth hormone level were higher in asphyxiated preterm babies in comparison to term asphyxiated babies. The elevated growth hormonal level in birth asphyxia had been explained on the basis of stress.

G.D. Lakshman Rajesh et al in his study measured growth hormone levels in 33 umbilical cord blood samples.

Babies with congenital malformation, hypoxic ischemic encephalopathy (HIE), intra uterine infections, still births, babies born to diabetic or eclamptic mothers were excluded from the study.

Babies were divided into three groups : Group A included term babies with birth weight > 2500 gms, Group B included term babies with birth weight < 2500 gms and Group C consisted of preterm babies.

There were 18 newborns in Group A, 9 in Group B, and 6 in Group C. The cord blood growth hormone ranged from 9.29 to 197 ng/ml. The cord blood growth hormone levels in Group A ranged from 9.29 to 68.11 ng/ml with a mean of 28.1 and standard deviation of 12.83 ng/ml. The levels in Group B ranged from 28.6 to 197 ng/ml with a mean of 76.8, a standard deviation of 55.7 ng/ml. In Group C, values ranged from 28.6 to 105.4 ng/dl with a mean of 72.5 and standard deviation of 29.4 ng/dl.

There was significant difference in between growth hormone levels in Group A and Group B ($p < 0.01$). The levels in group A were significantly lower than Group C ($p < 0.01$). However, the

difference in levels between Group B and Group C was not statistically significant ($p < 0.01$).

Growth hormone levels in preterm babies and low birth weight were higher as compared to term babies > 2500 gms indicating that growth hormone has an important role to play in intrauterine growth along with other growth promoting factors.

Material & Methods

Material and methods

This study was conducted in the department of Pediatrics, M.L.B. Medical College, Jhansi in active collaboration with the department of Obstetrics and Gynaecology and department of Microbiology, M.L.B. Medical College, Jhansi.

Criteria for selection of cases : Newborns delivered in the department of Obstetrics and Gynaecology, MLB Medical College, Jhansi, both term and preterms, were included in the study.

Neonates with < 30 weeks of gestational age, asphyxiated newborns, neonates with congenital malformation .and those with high risk factors for prematurity were excluded.

Neonates with mothers having cardiac, renal, pulmonary or other systemic disease were excluded from the study.

History and examination of newborns : A complete medical and obstetric history including perinatal, natal, postnatal events, type of delivery, maternal or fetal complication were evaluated.

The gestational age was assessed by first day of last menstrual period (LMP), confirmation was done by New Ballard Score.

All newborns were subjected to anthropometric examination:

1. Weight : Birth weight was taken on an electronic type of weighing scale with minimum measurement of 10 gm.

2. Length : Length was taken with child supine on an infantometer.

The head was held firmly in position against head board, legs straightened keeping feet at right angles to legs.

3. Head circumference : Maximum occipito - frontal circumference from the occipital protuberance to the forehead.

Head circumference was measured by a narrow non-stretchable measuring tape with minimum measurement of 0.1 cm.

New Ballard scoring for gestational age estimation of neonates

Neuromuscular maturity

	-1	0	+1	2	3	4	5
Posture							
Square window (wrist)							
Arm recoil							
Popliteal angle							
Scarf sign							
Heel to ear							

Maturity Rating

Score	Weeks
-10	20
-5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

Physical maturity.

	-1	0	1	2	3	4	5
Skin	Sticky, Friable transparent	Gelatinous red, translucent	Smooth, pink visible veins	Superficial peeling &/or rash, few veins	Cracking, pale areas, rare veins	Parchment deep cracking, no vessels	Leathery, cracked, wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel-toe, 40-50mm— 1<40mm—2	< 50 mm No crease	Faint Red Mark	Anterior transverse crease only	Creases on anterior 2/3	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola no bud	Stripped areola, 1–2 mm bud	Raised areola, 3–4 mm bud	Full areola, 5–10 mm bud	
Eye/ear	Lids fused loosely (-1) Tightly (-2)	Lids open pinna flat stays folded	Slightly curved pinna soft slow recoil	Well curved pinna, soft but ready recoil	Formed & firm instant recoil	Thick cartilage, ear stiff	
Genitals							
Male	Scrotum flat, smooth	Scrotum empty, faint rugae	Testis in upper canal	Testis descending, few rugae	Testis down, good rugae	Testis pendulous, deep rugae	
Female	Clitoris prominent	Prominent Clitoris, small labia Minora	Prominent Clitoris, enlarging Minora	Majora & minora equally prominent	Majora large, minora small	Majora cover clitoris & minora	

Collection of blood samples : 2 ml of non oxylated umbilical cord venous blood was taken at the time of delivery.

Growth hormone estimation : In this study serum GH assay was done by ELISA method by using microplate immuno enzymometric assay kit.

Preparation of serum assay : 1 ml of non oxylated blood was taken in a glass vial or tube. The blood was allowed to clot at room temperature. It was than centrifuged to separate serum from the cells. Serum sample was refrigerated at 2-8°C for a maximum period of 5 days. In case of not being assayed within this time, sample was stored at -20°C for upto 30 days.

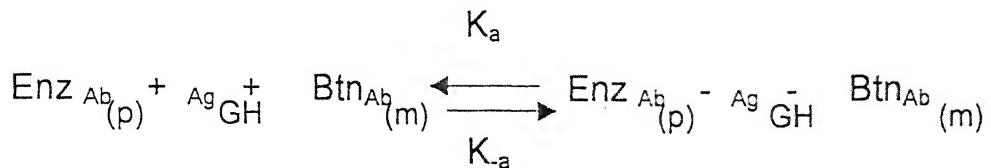
Principal of assay

Immunoenzymometric assay: The essential reagents required for this assay include high affinity and specificity antibodies (enzyme and immobilized), with different and distinct epitope recognition, in excess and native antigen. In this procedure, the immobilization had taken place during the assay at the surface of a microplate well through the interaction of streptavidin coated on the well and exogeneously added biotinylated monoclonal anti growth hormone antibody.

Upon mixing monoclonal biotinylated antibody, the enzyme labelled antibody and a serum containing the native antigen, reaction had occurred between the native antigen and the

antibodies without competition or steric hindrance, to form a soluble sandwich complex.

The interaction is illustrated by the following equation:



$\text{Bttn}_{\text{Ab}}_{(m)}$ = Biotinylated monoclonal antibody (Excess quantity)

$\text{Ag } \text{GH}$ = Native antigen (Variable quantity)

$\text{Enz } \text{Ab}_{(p)}$ = Enzyme labelled polyclonal antibody (Excess quantity)

Antigen-antibodies sandwich complex.

Rate constant of association

Rate constant dissociation

$\text{Enz } \text{Ab}_{(p)} - \text{Ag } \text{GH} \quad \text{Bttn}_{\text{Ab}}_{(m)}$ = Antigen-antibodies sandwich
Complex

K_a = Rate constant of association.

K_d = Rate constant of dissociation.

Simultaneously, the complex was deposited to the well through the high affinity reaction of streptavidin and biotinylated antibody. This interaction is illustrated below:

$\text{Enz } \text{Ab}_{(p)} - \text{Ag } \text{GH} \quad \text{Bttn}_{\text{Ab}}_{(m)} + \text{Streptavidin c.w.} \rightarrow \text{immobilized Complex}$

Streptavidin c.w. = Streptavidin immobilized on well.

Immobilized complex = Sandwich complex bound to the solid surface.

After equilibrium had been attained the antibody bound fraction was separated from unbound antigen by decantation or aspiration. The enzyme activity in the antibody bound fraction was directly proportional to the native antigen concentration. By utilizing several different serum reference of known antigen values, a dose response curve was generated from which the antigen concentration of unknown was ascertained.

Test procedure

Before proceeding with the assay, all reagents, serum references and controls were brought to room temperature.

1. Microplate wells were formed for each serum reference, control and patient specimen to be assayed in duplicate:
2. 0.050 ml (50 μ l) of the appropriate serum reference, control or specimen was pipetted into the assigned well.

3. 0.100 ml (100 μ l) of the biotinylated / enzyme labelled antibodies was added to each well. It is very important to dispense all reagents close to the bottom of the coated well.
4. Microplate wells were swirled gently for 20-30 seconds to mix and were kept covered.
5. The microplate wells were incubated for 60 minutes at room temperature.
6. Contents of the microplate wells were discarded by decantation or aspiration. If decanted, then plates were dried by taping and blotting with absorbent paper.
7. 300 μ l of wash buffer was added, decanted or aspirated and dried as above. This procedure was repeated two additional times for a total of three washes.
8. 0.100ml (100 μ l) of working substrate solution was added to all wells. Always reagents were added in the same order to minimize reaction time differences between wells and were incubated at room temperature for fifteen minutes.
9. 0.050 ml (50 μ l) of stop solution was added to each well and microplate wells were swirled gently for 15-20 seconds to mix.

Reagents were always added in the same order to minimize reaction time difference between wells.

10. The absorbance was read in each well at 450nm by microplate ELISA reader. The results were read within thirty minutes of adding the stop solution.

With the help of dose response curve obtained by serum reference of known antigen values, growth hormone levels for respective absorbance of unknown serum was obtained.

Observations

Observations

The present study was conducted on 40 neonates, delivered in the Department of Obstetrics and Gynaecology, M.L.B. Medical College, Jhansi from October 2003 to October 2004.

The study comprised of, both normal birth weight (> 2.5 Kg) and low birth weight (< 2.5 Kg) neonates. Low birth weight group was further divided into preterm (< 37 weeks) and full term small for gestational age neonates ($< 10^{\text{th}}$ centile for gestational age). There were no preterm small for gestational age cases in our study.

Preterm group was again divided into neonates with gestational age of 30 – 33 weeks and 34 – 37 weeks respectively. None of the neonates included in the study had signs of birth asphyxia.

Table 1

Distribution of cases according to birth weight

Birth Weight (Kg)	Normal Birth Weight (> 2.5 Kgs) (group a)	Low Birth Weight (< 2.5 Kgs) (group b)	
		Preterm	SGA
Number of cases (n)	20	10	10

Out of 40 cases, 20 were of more than 2.5 Kg (Group a) and 20 cases were of low birth weight (Group b) (Table 1).

Low birth weight neonates were again divided into preterm and small for gestational age neonates. Our study comprised of 10 preterm and 10 small for gestational age cases.

Table 2

Distribution of preterm cases according to gestational age

Gestational age	30 – 33 weeks	34 – 37 weeks
No. of cases	5	5

Preterm cases were again divided on the basis of gestational age into neonates born at 30 – 33 weeks and those born at 34 – 37 weeks of age. Each group comprised of 5 cases. Preterm cases < 30 weeks were excluded from the study.

Table 3

Distribution of cases according to sex

	Male (m)	Female (f)
Normal birth weight (Group a)	10	10
Low birth weight (Group b)	10	10

Table 3 shows the distribution of cases according to sex. There were 10 male and 10 female cases in both group 'a' and group 'b'.

Table 4

Growth hormone levels (ng/ml) in relation to birth weight

	(n)	Range	Mean ± S.D.
Normal birth weight (a)	20	12.5 – 64	35.65 ± 13.98
Low birth weight (b)	20	25 – 120.5	56.91 ± 29.45

Table 5

Statistical analysis of Growth hormone levels in relation to birth weight

't' value ('t' _{ab})	d-f	'p' value ('p' _{ab})	Significance
3.18	38	< 0.001	Highly significant

Table 4 depicts the growth hormone levels (ng/ml) in both the normal birth weight and low birth weight neonates. Neonates in group 'a' showed a mean value of 35.65 ng/ml with a range of 12.5 – 64 ng/ml and standard deviation of 13.98 ng/ml. The mean growth hormone level in group 'b' was 56.91 ng/ml with a range of 25 – 120.5 ng/ml and standard deviation of 29.45 ng/ml.

Table 6**Growth hormone levels (ng/ml) in full term newborns**

	(n)	Range	Mean ± S.D.
Full term AGA	20	12.5 – 64	35.65 ± 13.98
Full term SGA	10	25 – 120.5	58.4 ± 28.56

Table 7**Statistical analysis of growth hormone levels in fullterm
newborns**

't' value ('t'As)	d-f	'p' value ('p'As)	Significance
2.37	28	< 0.05	Significant

Table 6 depicts the levels of growth hormone in fullterm appropriate for age and fullterm small for gestational age cases. Mean Growth hormone level in fullterm AGA group was 35.65 ± 13.98 ng/ml with a range of 12.5 – 64 ng/ml. Growth hormone level in fullterm SGA cases was 58.4 ± 28.56 ng/ml with a range of 25 – 120.5 ng/ml.

Table 8
Growth hormone levels (ng/ml) in preterm and small for gestational age cases

	(n)	Range	Mean ± S.D.
Pre term	10	30.5 – 98	53.5 ± 24.63
SGA	10	25 – 120.5	58.4 ± 28.56

Table 9
Statistical significance of growth hormone levels (ng/ml) between preterm and small for gestational age neonates.

't' value ('t'ps)	d-f	'p' value ('p'ps)	Significance
0.411	18	> 0.05	Not Significant

Table 8 depicts the growth hormone levels among the subgroups of low birth weight neonates, i.e. the preterm and SGA cases. Preterm newborns had a mean growth hormone value of 53.5 ± 24.63 ng/ml with a range of 30.5 – 98 ng/ml. Small for date neonates had mean GH value of 58.4 ± 28.56 ng/ml with a range of 25 – 120.5 ng/ml.

Table 10**Growth hormone levels (ng/ml) in relation to gestational age**

	(n)	Range	Mean \pm S.D.
Full term (F)	20	12.5 – 64	35.65 \pm 13.98
Pre term (< 37 weeks) (P)	10	30.5 – 98	53.5 \pm 24.63

Table 11**Statistical significance of growth hormone levels in relation to gestational age**

't' value ('t' _{FP})	d-f	'p' value ('p' _{FP})	Significance
2.16	28	< 0.05	Significant

Table 10 shows the growth hormone levels in relation to gestational age. Full term neonates with weight > 2.5 Kg showed growth hormone level of 35.65 ± 13.98 with a range of 12.5 – 64 ng/ml. Preterm neonates (< 37 weeks) showed growth hormone level of 53.5 ± 24.63 with a range of 30.5 – 98 ng/ml.

Table 12
Growth hormone levels in preterms

Gestational age	(n)	Range	Mean ± S.D.
30 – 33 weeks	5	30.5 – 87.0	54.25 ± 24.14
34 - 37 weeks	5	31.5 – 98	51.7 ± 25.05

Table 13
Statistical significance of growth hormone levels in preterms

't' value ('t' _{ab})	d-f	'p' value ('p' _{ab})	Significance
0.229	8	> 0.05	Not significant

Table 12 shows the growth hormone levels in preterm neonates according to gestational age range (Table 2). It shows that mean level of growth hormone in neonates with 30 – 33 weeks was 54.25 ± 24.14 with a range of 30.5 – 87 ng/ml. In neonates with 34 – 37 weeks the mean growth hormone level was 51.7 ± 25.05 with a range of 31.5 – 98 ng/ml.

Table 14

Growth hormone level (ng/ml) according to sex

	(n)	Range	Mean ± S.D.
Normal birth weight (a)			
Male	10	12.5 – 64	36.0 ± 14.33
Female	10	13.5 – 61	35.4 ± 13.42
Low birth weight (b)			
Male	10	30.5 – 116.5	54.65 ± 28.13
Female	10	25 – 120.5	59.35 ± 30.2

Table 15

**Statistical significance of growth hormone level (ng/ml)
according to sex**

	't' value	d-f	'p' value	Significance
Group a	0.39	18	> 0.05	Not significant
Group b	0.360	18	> 0.05	Not significant

Table 14 reviews the growth hormone values according to sex distribution (Table 3). This data shows that in group 'a' the male cases had mean growth hormone value of 36.0 ± 14.33 with a range of 12.5 – 64 ng/ml. Female cases in group 'a' had mean levels of 35.4 ± 13.42 with a range of 13.5 – 61 ng/ml.

In group 'b' the male cases had mean growth hormone value of 54.65 ± 28.13 with a range of 30.5 – 116.5 ng/ml. Female cases in group 'b' had mean levels of 59.35 ± 30.2 with a range of 25 – 120.5 ng/ml.

Table 16**Growth hormone levels (ng/ml) according to length**

Length (cm)	(n)	GH Range	Mean ± S.D.
39.0 – 42 (a)	8	35 – 120.5	59.7 ± 15.55
42.1 – 45 (b)	9	25 – 98.0	51.3 ± 13.46
45.1 – 48 (c)	9	30.5 – 76	40.4 ± 13.90
> 48 (d)	15	21 – 63.5	38.3 ± 12.92

Table 17**Statistical significance of growth hormone levels (ng/ml)****according to length**

't'	't' value	d-f	'p' value	Significance
't _{ab} '	1.18	15	> 0.05	Not significant
't _{ac} '	2.69	15	< 0.02	Significant
't _{bc} '	1.689	16	> 0.05	Not significant
't _{bd} '	2.32	22	< 0.05	Significant
't _{cd} '	0.368	22	> 0.05	Not significant
't _{ad} '	4.752	21	< 0.01	Significant

Table 16 shows the distribution of study cases according to length at birth. Neonates included in this study had a length range of 39 – 50.5 cm with a mean of 45.85 cm.

The neonates were grouped according to length range into four groups namely a, b, c, d respectively. The mean growth hormone values in group 'a' were 59.7 ± 15.55 with a range of 35 – 120.5 ng/ml. In group 'b' the mean levels were 51.3 ± 13.46 with a range of 25 – 98 ng/ml. In group 'c' the mean levels were 40.4 ± 13.90 with a range of 30.5 – 76 ng/ml. In group 'd' the mean values turned out to be 38.3 ± 12.92 with a range of 21 – 63.5 ng/ml.

Table 18

Growth hormone levels in relation to head circumference

Head circumference (cm)	(n)	GH Range	Mean \pm S.D.
29.5 – 31 (a)	8	32 – 120.5	58.7 ± 15.02
31.1 – 32.5 (b)	10	23 – 92.0	50.3 ± 13.10
32.6 – 34 (c)	8	32 – 80.5	41.9 ± 13.80
> 34 (d)	14	21 – 61.5	38.7 ± 12.6

Table 19

Statistical analysis of growth hormone levels in relation to head circumference

't'	't' value	d-f	'p' value	Significance
't _{ab} '	1.23	16	> 0.05	Not significant
't _{ac} '	2.33	14	< 0.05	Significant
't _{bc} '	1.35	16	> 0.05	Not significant
't _{bd} '	2.17	22	< 0.05	Significant
't _{cd} '	0.561	20	> 0.05	Not significant
't _{ad} '	3.18	20	< 0.01	Significant

Head circumference of all the studied cases were measured and were grouped according to range of head circumference into four groups namely a, b, c, d respectively.

On viewing table 18 we find the levels in group 'a' to be 58.7 ± 15.02 with a range of 32 – 120.5 ng/ml. Group 'b' had mean value of 50.3 ± 13.10 with a range of 23 – 92 ng/ml. Group 'c' had mean values of 41.9 ± 13.80 with a range of 32 – 80.5 ng/ml. In group 'd' the mean values were 38.7 ± 12.6 with a range of 21 – 61.5 ng/ml.

Discussion

Discussion

The present study was conducted on 40 neonates, delivered in the Department of Obstetrics and Gynaecology, M.L.B. Medical College, Jhansi from October 2003 to October 2004.

The present study was undertaken with the following aims :

3. To measure the growth hormone levels in full-term and pre-term neonates.
4. To study the relationship of gestational age, sex, birth weight, length and head circumference with growth hormone levels in neonates.

The present study comprised of 40 neonates, out of which, 20 neonates were normal birth weight and 20 were low birth weight. Low birth weight neonates were again divided into preterm and fullterm small for gestational age neonates (Table 1).

Cases were divided according to sex into male and female subgroups in both normal and low birth weight (Table 3). Cases were divided into subgroups according to range of length and head circumference (Table 16, 18).

Some studies have been conducted on growth hormone levels in normal full term and preterm babies by different workers, with varying results. There is a paucity of studies in Indian literature on this subject. We could not find any other study which relates growth hormone level to length and head circumference of newborns.

In our study, neonates in group 'a' (birth weight > 2.5 Kg) showed a mean value of 35.65 ng/ml with a range of 12.5 – 64 ng/ml and standard deviation of 13.98 ng/ml. The mean growth hormone level in group 'b' (birth weight < 2.5 Kg) was 56.91 ng/ml with a range of 25 – 120.5 ng/ml and standard deviation of 29.45 ng/ml (Table 4).

On statistical analysis, the growth hormone levels in low birth weight group was found to be significantly higher ($p < 0.001$) than in neonates with normal birth weight (Table 5).

Naguib et al (1987), in their study found growth hormone value in normal birth weight cases to be 13.7 ± 8.5 ng/ml. These values are somewhat lower than our findings.

Kapoor et al (1996), estimated growth hormone levels by radioimmunoassay method using code RIAK-3 kits. They found

values in full term neonates to be 25.2 ± 3.8 ng/ml, which are lower than that of our observed values.

G.D. Lakshman Rajesh et al (2000), measured growth hormone values using radioimmunoassay kit, Wallac 1470 wizard Auto Gamma Counter. They observed that growth hormone values in babies with weight > 2.5 Kg were 28.1 ± 12.83 ng/ml. These values are somewhat lower than our observed values. In term babies with weight < 2.5 Kg it was 76.8 ± 55.7 ng/ml, which are higher than our findings.

In our endeavour the growth hormone levels in fullterm appropriate for age and fullterm small for gestational age cases were compared. Mean Growth hormone level in fullterm AGA group was 35.65 ± 13.98 ng/ml with a range of 12.5 – 64 ng/ml. Growth hormone level in fullterm SGA cases was 58.4 ± 28.56 ng/ml with a range of 25 – 120.5 ng/ml (Table 6).

On statistical analysis, we found that growth hormone levels in fullterm small for gestational age cases were significantly higher than fullterm appropriate for gestational age cases ($'p'_{AS} < 0.05$) (Table 7).

Naguib et al (1987), measured growth hormone values using immunoreactive method. In their study growth hormone values in fullterm AGA cases were 13.7 ± 8.5 ng/ml, which are somewhat lower than our findings. In small for gestational age cases, the value was 17.3 ± 12 ng/ml, which is also lower than our findings.

G.D. Lakshman Rajesh et al (2000), in his study found levels in term AGA group to be 28.1 ± 12.83 ng/ml, which are lower than in our study. In his study, the levels in term newborns with birth weight < 2.5 Kg were 76.8 ± 55.7 ng/ml, which are slightly higher than our observed values.

Table 8 depicts the growth hormone levels among the subgroups of low birth weight neonates, i.e. the preterm and SGA cases. Preterm newborns had a mean growth hormone value of 53.5 ± 24.63 ng/ml with a range of 30.5 – 98 ng/ml. Small for date neonates had mean GH value of 58.4 ± 28.56 ng/ml with a range of 25 – 120.5 ng/ml.

On statistical analysis of the above data, we observed that growth hormone levels in preterm cases were not significantly different from small for gestational age cases ($p > 0.05$) (Table 9).

In a study by Naguib et al (1987), the growth hormone values in preterm newborns were 23 ± 11 ng/ml and in SGA newborns, it was 17.3 ± 12 ng/ml. These are lower than our observed values.

Kapoor et al (1996), in their study found levels in preterm cases to be 37.3 ± 4.5 ng/ml. These values were also lower than ours'. They didn't consider SGA cases in their study.

G.D. Lakshman Rajesh et al (2000), observed that mean value in preterm cases was 72.5 ± 29.4 ng/ml, whereas, in fullterm small for gestational age cases it was 76.8 ± 55.7 ng/ml. These values are higher than those in our study.

As evident from observations of Table 10 the growth hormone levels in fullterm neonates with weight > 2.5 Kg were 35.65 ± 13.98 with a range of 12.5 – 64 ng/ml. Preterm neonates (< 37 weeks) showed growth hormone level of 53.5 ± 24.63 with a range of 30.5 – 98 ng/ml.

From the data tabulated in table 11 we can say that growth hormone levels in preterm neonates were significantly higher than full term neonates (' $p'_{FP} < 0.05$).

Cornblath et al (1964), observed that growth hormone value in fullterm neonates was 66 ± 72.2 ng/ml (9 – 320), which are lower

than our observed values. In their study, the value in preterm neonates were 59 ± 15.7 (38 – 83) ng/ml. This is lower than the values of our study.

Naguib et al (1987), found that term cases had values of 13.7 ± 8.5 ng/ml, whereas, preterms had 23 ± 11 ng/ml. These observations are lower than in our study. Stubbe and Wolf (1970), observed the values in fullterm newborns to be 45.7 ± 4.8 ng/ml.

Kapoor et al (1996), in their study found that term neonates were having values of 25.2 ± 3.8 ng/ml, whereas preterms had 37.3 ± 4.5 ng/ml, which are lower than that of our study.

G.D. Lakshman Rajesh et al (2000), found that in fullterm neonates levels were 28.1 ± 12.83 ng/ml, which are lower than ours. In preterm newborns, they found the levels to be 72.5 ± 29.4 ng/ml, which are higher than in our study.

On study of growth hormone levels in preterm group according to gestational age range we found the mean levels of growth hormone in neonates with 30 – 33 weeks to be 54.25 ± 24.14 with a range of 30.5 – 87 ng/ml. In neonates with 34 – 37 weeks the mean growth hormone level was 51.7 ± 25.05 with a range of 31.5 – 98 ng/ml (Table 12).

On analyzing the above data statistically we found that the mean growth hormone levels between these two subgroups are not significantly different (Table 13). It shows that growth hormone values are not significantly affected by gestational age range within the preterm group.

The distribution of growth hormone values according to sex distribution showed that in group 'a' the male cases had mean growth hormone value of 36.0 ± 14.33 with a range of 12.5 – 64 ng/ml. Female cases in group 'a' had mean levels of 35.4 ± 13.42 with a range of 13.5 – 61 ng/ml. Similarly, in group 'b' the male cases had mean growth hormone value of 54.65 ± 28.13 with a range of 30.5 – 116.5 ng/ml. Female cases in group 'b' had mean levels of 59.35 ± 30.2 with a range of 25 – 120.5 ng/ml (Table 14).

On statistical analysis of above values we found that growth hormone values were not significantly different between male and female cases in weight matched groups (Table 15).

Cornblath et al (1964), also did not find any significant difference between male and female cases in weight matched groups.

In our study neonates were divided according to length range and the distribution showed that neonates included in this study had a length range of 39 – 50.5 cm with a mean of 45.85 cm.

The neonates were grouped according to length range into four groups namely a, b, c, d respectively. The mean growth hormone values in group 'a' were 59.7 ± 15.55 with a range of 35 – 120.5 ng/ml. In group 'b' the mean levels were 51.3 ± 13.46 with a range of 25 – 98 ng/ml. In group 'c' the mean levels were 40.4 ± 13.90 with a range of 30.5 – 76 ng/ml. In group 'd' the mean values were 38.3 ± 12.92 with a range of 21 – 63.5 ng/ml (Table 16).

On statistical analysis, we observed that there was significant difference in growth hormone levels between group 'a' and 'c', group 'b' and 'd' as well as group 'a' and 'd'. The difference in values was not significant between group 'a' and 'b', group 'b' and 'c' and also between group 'c' and 'd'.

Head circumference of all the studied cases were measured and were grouped according to range of head circumference into four groups as follows : group 'a' had a mean level of 58.7 ± 15.02 with a range of 32 – 120.5 ng/ml, group 'b' showed mean value of 50.3 ± 13.10 with a range of 23 – 92 ng/ml., group 'c' had mean

values of 41.9 ± 13.80 with a range of 32 – 80.5 ng/ml and in group 'd' the mean values were 38.7 ± 12.6 with a range of 21 – 61.5 ng/ml (Table 18).

On statistical analysis we found that growth hormone values were not significantly different between group 'a' and 'b' , group 'b' and 'c' as well as group 'c' and 'd'. We observed that there was significant difference in growth hormone levels between group 'a' and 'c', group 'b' and 'd' as well as group 'a' and 'd' ($'p'_{ac} < 0.05$, $'p'_{ad} < 0.01$, $'p'_{bd} < 0.05$).

We could not find any other study which relates growth hormone levels in cord blood to length and head circumference of newborns.

Kaplan et al (1972), suggested that, by mid gestation, with appearance of hypothalamic nuclei and electrical activity of diencephalon, secretion of growth hormone releasing factor might occur with resultant unrestrained release of growth hormone by fetal pituitary. By late gestation, the neural inhibitory influences become operative and could lead to decreased growth hormone releasing factor and growth hormone secretion.

Naguib et al (1987), suggested that growth hormone levels in neonates were a reflection of not only gestation age, but also birth weight. When term infants were categorized according to birth weight, there was an overall effect on growth hormone. On comparing term with preterm infants, there was a difference in these hormonal values. Growth hormone levels were higher in premature neonates and apgar scores in this group were lowest. Although, this may reflect the gestational age of the newborn infant, stress cannot be excluded from consideration.

It is evident from our observation on growth hormone levels, and from the observations of other workers regarding growth hormone values in these groups of neonates, that there was some variation of the results in different studies, which may be possibly because of different populations studied and individual analytic laboratory differences.

Summary

Summary

The present study entitled "Growth hormone levels in newborns in relation to gestational age and anthropometric indices" was conducted in the Department of Pediatrics with assistance from the Department of Microbiology and Department of Gynaecology, M.L.B. Medical College, Jhansi. The study period extended from October 2003 to October 2004.

In our study a total of 40 cases were taken, of which 20 were more than 2.5 Kgs and 20 were low birth weight. Both groups were divided on the basis of sex. Low birth weight group was divided into preterm and small for gestational age neonates. Preterm neonates were again divided according to gestational age into neonates with 30 – 33 weeks and those with 34 – 37 weeks.

According to gestational age there were 20 full-term normal birth weight, 5 preterms with 30 – 33 weeks and 5 with 34 – 37 weeks. On the basis of sex there were 10 males with weight more than 2.5 Kg and 10 males less than 2.5 Kg. Similarly, there were 10 females with weight more than 2.5 Kg and 10 females less than 2.5 Kg.

Blood sample from umbilical vein was taken just after birth, and serum was separated within one hour of collection. Serum was subjected to growth hormone measurement by Mono bind ELISA kit.

- ❖ In newborns with birth weight more than 2.5 Kg growth hormone level was 35.65 ± 13.98 with a range of 12.5 – 64 ng/ml. In the low birth weight group the growth hormone level was 56.91 ± 29.45 ng/ml with a range of 25 – 120.5 ng/ml ($p < 0.001$). Growth hormone level were significantly higher in the low birth weight group as compared to neonates with normal birth weight.
- ❖ Mean Growth hormone level in fullterm AGA group was 35.65 ± 13.98 ng/ml with a range of 12.5 – 64 ng/ml. Growth hormone level in fullterm SGA cases was 58.4 ± 28.56 ng/ml with a range of 25 – 120.5 ng/ml, which on statistical analysis showed, that growth hormone levels in fullterm small for gestational age cases were significantly higher than fullterm appropriate for gestational age cases (' $p'_{AS} < 0.05$).
- ❖ The growth hormone levels among the subgroups of low birth weight neonates, i.e. the preterm and SGA cases were 53.5 ± 24.63 (30.5 – 98) ng/ml and 58.4 ± 28.56 (25 – 120.5) ng/ml.

Growth hormone level in preterm cases were not significantly different from small for gestational age cases ($p > 0.05$).

- ❖ The growth hormone levels in fullterm neonates with weight > 2.5 Kg were 35.65 ± 13.98 with a range of $12.5 - 64$ ng/ml. Preterm neonates (< 37 weeks) showed growth hormone level of 53.5 ± 24.63 with a range of $30.5 - 98$ ng/ml. The growth hormone levels in preterm neonates were significantly higher than in full term neonates (" $p'_{FP} < 0.05$ ").
- ❖ In our study the mean growth hormone levels in preterm neonates with $30 - 33$ weeks gestation were 54.25 ± 24.14 ($30.5 - 87$) ng/ml. In neonates with $34 - 37$ weeks gestation mean growth hormone level was 51.7 ± 25.05 with a range of $31.5 - 98$ ng/ml. Thus, the mean growth hormone levels between these two subgroups are not significantly different. It shows that growth hormone values are not significantly affected by gestational age range within the preterm group.
- ❖ As evident from our study, in neonates with birth weight > 2.5 Kg the male cases had mean growth hormone value of 36.0 ± 14.33 (range $12.5 - 64$) ng/ml. Females on the other hand had mean levels of 35.4 ± 13.42 with a range of $13.5 - 61$ ng/ml. In cases

with weight < 2.5 Kg, male neonates had mean growth hormone value of 54.65 ± 28.13 with a range of 30.5 – 116.5 ng/ml and female cases had mean levels of 59.35 ± 30.2 with a range of 25 – 120.5 ng/ml. Growth hormone values were not significantly different between the two sexes in weight matched neonates.

❖ Neonates included in this study had a length range of 39 – 50.5 cm with a mean of 45.85 cm. The neonates were grouped according to length range into four groups namely a, b, c, d respectively. The mean growth hormone values in group 'a' were 59.7 ± 15.55 with a range of 35 – 120.5 ng/ml. In group 'b' the mean levels were 51.3 ± 13.46 with a range of 25 – 98 ng/ml. In group 'c' the mean levels were 40.4 ± 13.90 with a range of 30.5 – 76 ng/ml. In group 'd' the mean values were 38.3 ± 12.92 with a range of 21 – 63.5 ng/ml.

We observed that there was significant difference in growth hormone levels between group 'a' and 'c', group 'b' and 'd' as well as group 'a' and 'd'. The difference in values was not significant between group 'a' and 'b', group 'b' and 'c' and also between group 'c' and 'd'.

- ❖ While studying the relation of growth hormone levels to head circumference of neonates, we categorized the cases according to increasing head circumference range into four groups a, b, c, d respectively. Group 'a' showed mean values of 58.7 ± 15.02 (32 – 120.5) ng/ml. Group 'b' had values of 50.3 ± 13.1 (23 – 92) ng/ml. Group 'c' showed the levels of 41.9 ± 13.8 (32 – 80.5) ng/ml and group 'd' had mean values of 38.7 ± 12.6 with a range of 21 – 61.5 ng/ml. On statistical analysis we observed that the difference between group 'a' and 'b' as well as between group 'b' and 'c' was not statistically significant, whereas significant difference was observed on comparing group 'a' and 'd' ($p_{ad} < 0.01$) as well as between group 'b' and 'd' ($p_{bd} < 0.05$).
- ❖ We observed that there was a significant difference in growth hormone values at the two ends of the spectrum of length and head circumference seen in our study. There was an inverse relationship between length and head circumference on one hand and growth hormone levels on the other.

Conclusion

Conclusions

From the data presented above the following conclusions may be drawn:

- ❖ Growth hormone values were significantly higher in low birth weight group than in fullterm neonates with birth weight above 2.5 Kg.
- ❖ Growth hormone values were significantly higher in preterm newborns than fullterm appropriate for gestational age cases.
- ❖ Among the low birth weight group there was no statistically significant difference in growth hormone levels between fullterm small for gestational age and preterm neonates..
- ❖ There was no significant difference in two groups of preterm newborns (gestational age 30 – 33 weeks and 34 – 37 weeks).
- ❖ There was no statistically significant difference in two sexes in both the groups, i.e. low birth weight neonates and those above 2.5 Kg birth weight.
- ❖ There was a significant difference in growth hormone values at the two ends of the spectrum of length and head circumference in our study. There was an inverse relationship between length and

head circumference on one hand and growth hormone levels on the other.

It suggests that, growth hormone levels in neonates were a reflection of not only gestational age but also birth weight.

Bibliography

Bibliography

1. Abrams RL, ML Parker, S Balanco, S Reichlin and WH Daughaday, 1966 : Hypothalamic regulation of growth hormone secretion. *Endocrinology*, 78: 605.
2. Alpert LC, Brawer JR, Patel YC et al : Somatostatinergic neurons in anterior hypothalamus: immunohistochemical localization. *Endocrinology*, 1976; 98: 255 - 258.
3. Anastasia varvarigou, Apostolos G Vagenakis, Maria Makri, Constantinos Frimos and Nicholas Berans : Prolactin and growth hormone in perinatal asphyxia. *Biol Neonate*, 1996: 69: 76 - 83.
4. Asa SL, Kovacs K, Laszlo FA et al : Human fetal adenohypophysis. Histologic and immunocytochemical analysis. *Neuro endocrinology*, 1986; 43: 308 - 316.
5. Asa SL, Kovacs K: Functional morphology of the human fetal pituitary (review). *Pathol Annu* 1984; 19(pt1): 275 - 315.
6. Auebert ML, J Sistek and H Bossart, 1972 : Fetal growth hormone in utero in the perinatal period. *Acta Endocrinol In press.*

7. Ballard JL, Khoury JC, Wedig K et al : New Ballard score; expanded to include extremely premature infants. *J Pediatr*, 1991, 119: 417 - 423.
8. Barinaga M, Yamonoto G, Rivier C et al : Transcriptional regulation of growth hormone gene expression by growth hormone releasing factor. *Nature*, 1983; 306: 84 - 85.
9. Baumann G, Shaw MA, Marimee TJ: Decreased growth hormone binding protein in pygmy plasma (abstract). *Clin Res*, 1988; 36: 551A.
10. Berelowitz M, Szabo M, Frohman LA et al : Somatomedin-c mediates growth hormone negative feedback by effects on both the hypothalamus and pituitary. *Science* 1981; 212: 1279 - 1281.
11. Buchanan CR, Maheshwari HG, Norman MR et al: Laron type dwarfism with apparently normal high affinity serum growth hormone-binding protein. *Clin Endocrinol (oxf)*, 1991; 35: 179 - 185.
12. Carlson A, 1959 : The occurrence, distribution and physiological role of catecholamines in the nervous system. *Pharmacol Rev*, 11: 490.

13. Chez RA, D L Hutchinson, H Salazar and DR Mintz, 1970: Some effects of fetal and maternal hypophysectomy in pregnancy. *AM J Obstet Gynecol*, 169, 643.
14. Clemons DR, Van Wyk JJ : Somatomedin: Physiology controls and effects on cell proliferation. In Basen R. *Handbook of Experimental Pharmacology*, Berl Springer Verlag. 161 - 207, 1981.
15. Cooke NE, Ray J, Watson MA et al : Human growth hormone gene and the highly homologous growth hormone variant gene display different splicing patterns. *J Clin Invest*, 1988, 82 : 270 - 275.
16. Cornblath MM, L Parker, SH Reisner, AE Forbes and WH Daughaday, 1965 : Secretion and metabolism of growth hormone in premature and fullterm infants. *J Clin Endocrinol Metab*. 25: 209.
17. Covell WP, 1927 : Growth of human prenatal hypothesis and the hypophyseal fossa. *Am J Anat*, 38 : 379.
18. Cunningham BC, Ultsch M, de Vos AM et al: Dimerization of the extracellular domain of the human growth hormone

- receptor by a single hormone molecule. *Science*, 1991; 254: 821 - 825.
19. Daikoku S, 1958: Studies on the human fetal pituitary: I Quantitative observation. *Tokushima J Exp Med*, 5: 200.
20. Daughaday WH, Phillips LS, Mueller MC: The effect of insulin and growth hormone on the release of somatomedin by the isolated rat liver. *Endocrinology*, 1976; 98 : 1214.
21. Daughaday WH, Reeder C : Synchronous activation of DNA synthesis in hypophysectomized rat cartilage by growth hormone. *J Lab Clin Med*, 1966; 68 : 357 - 368.
22. Daughady WH: Growth hormone and the somatomedins. Daughady WH Ed. *Endocrine control of growth*. New Y Elsevier North Holland, 1981.
23. de Vos Am, Ultsch M, Kossiakoff AA : Human growth hormone and extracellular domain of its receptor; crystal structure of the complex, *science*, 1992; 255: 306-312.
24. DeNoto FM, Moore OD, Goodman HM : Human growth hormone DNA sequence and m-RNA structure: possible alternative splicing. *Nuclic acids Res*, 1981; 9: 3719 - 3730.

25. Dubois P, 1968: Donnees ultrastructurales Sur l' ante hyopphyse d'un embryon humaine a la huitieme semaine de son development. CR Soc Biol, 162: 689.
26. Dunn JM 1966 ; Anterior pituitary and adrenal in a live born normocephalic infant. Amer J Obstet Gynecol, 96: 893.
27. Ellis ST, JS Beck and AR currie, 1966 : The cellular localization of growth hormone in the human foetal adenohypophysis. J Pathol Bacteriol 92: 179.
28. Gerich JE, Lorenzi M, Bier DM et al : Effects of physiologic levels of glucagon and growth hormone on human carbohydrate and lipid metabolism. Studies involving administration of exogenous hormone during suppression of endogenous hormone secretion with somatostatin. J Clin Invest, 1976; 57: 875 - 884.
29. Glick SM, J Roth, HS Yldow and SA Berson, Nature (London), 1998, 786, 1963.
30. Glueckman PD, Grumback MM, Kaplan SL : The neuroendocrine regulation and function of growth hormone and prolactin in the mammalian fetus (review). Endocr Rev, 1981; 2: 363 - 395.

31. Glueckman PD, Mueller PL, Kaplan SL, Rudolph Am, Grumback MM : Hormone ontogeny in the ovine fetus. I Circulating growth hormone in mid and late gestation. *Endocrinology*, 1979, 104; 162 -168.
32. Goodyer CG, Ontogeny of pituitary hormone secretion. In Collu R Ducharme JR. Guyda HJ eds, *Pediatric endocrinology*. New York: Raven press, 1989: 125 - 169.
33. Greenwood FC, WM Hunter and H Klopper, *Brit Med J*, 1:22, 1964.
34. Grumback MM, 1962 : Intracellular detection of hormones by immunochemical means. *Growth hormone*, Ciba Found Collog Endocrinol, 14: 373.
35. Hatasz B : Hypothalamo-anterior pituitary system and pituitary portal vessels. Imura H ed. *The pituitary gland*, 2nd ed. New York Raven, 1994: 1-28.
36. Heller H, *Etudes Neonatal*, 3:31, 1954.
37. Ikeda H, Suzuki J, Sasano N et al : The development and morphogenesis of the human pituitary gland. *Anat Embryol*. 1988; 178: 327-336.
38. Jost A: *Recent programme hormone Res*, 8: 379, 1953.

39. Kalkhoff R et al : Trans Ass Amer Physicians, 127: 270, 1964.
40. Kaplan SL and MM Grumback, J Clin Endocr, 24: 80, 1964.
41. Kaplan SL, MM Grumback and TH Shepard: Ontogenesis of human fetal hormones. J Clin Invest, 51: 3080-3092 (1972).
42. Kapoor RK, Mishra SK, Kumar Ajay, Agrawal CG: Growth Hormone in Birth Asphyxia, Indian Pediatrics, 34: 133 - 135, 1997.
43. Katz SH, APS Dhariwal and SM McCann, 1967: Effect of hypoglycemia on the content of pituitary growth hormone and hypothalamic growth hormone releasing factor in the rat. Endocrinology, 81: 333.
44. Kohler PO, BW O' malley, PL Rayford, MB Lipsett and WD Odell, 1967 : Effect of pyrogen on blood levels of pituitary trophic hormones observations on the usefulness of the growth hormone response in the detection of pituitary disease. J Clin Endocrinol Metab, 27: 219.
45. Koritnik DR, Humphrey WD, Kalten back CC, Dunn TG : Effects of maternal under nutrition on the development of the ovine fetus and the associated changes in growth hormone and prolactin. Biol Reprod, 1981: 24: 125-137.

46. Kostyo JL, Hotchkiss J, Knobil E : Stimulation of amino acid transport in isolated diaphragm by growth hormone added in vitro. Science 1959; 130: 1653 - 1656.
47. Krisch B : Hypothalamic and extrahypothalamic distribution of somatostatin - immunoreactive elements in the rat brain cell tissue. Res, 1978; 195: 499 - 513.
48. Krulich L and SM McCann, 1966 : Evidence for the presence of growth hormone releasing factor in blood of hypoglycemic hypophysectomized rats. Proc Soc Exptt Biol Med, 122: 668.
49. Lecham RM : Neuroendocrinology of pituitary hormone regulation. Endocrinol Metab Clin North AM, 1987,16:475-501.
50. Leung DW, Spencer SA, Cachianes G et al : Growth hormone receptor and serum binding protein purification, cloning and expression. Nature, 1987; 330: 537-543.
51. Marvin Cornblath, Mary L Parker, Solomon H Reisner, Audrey E Forbes and William H Daughaday, Secretion and metabolism of growth hormone in premature and full term infants. J Clin Endocr, 25: 209, (1965).

52. Mc Donald JW and Johnston MV : Physiological and pathophysiological roles of excitatory aminoacids during central nervous system development. Brain Res Rev, 1990;1541.
53. Meyer V and E Knobil, 1966 : Stimulation of GH secretion by vasopressin in the Rhesus monkey. Endocrinology, 79: 1016.
54. Milner RDG, AD Wright : Plasma glucose, nonesterified fatty acids, insulin and growth hormone response to glucagon in the newborn. Clin Sci, 32: 249 (1967).
55. Muller EE, S Sawano, A Arimeera and AV Schally, 1967 : Blockade of release of GH by brain nor epinephrine depletors. Endocrinology. 80: 471.
56. Nagashima K, Hidek Yagi, Shigoysui Suzuki: Takasi Noji, Histosi Yunoki, Takayosi Kuroume: Levels of growth hormone and growth hormone releasing factor in cord blood. Biological neonate. 49: 307-310, 1986.
57. Nanagas JC, 1925 : A comparison of the body dimension of an encephalic human fetuses with normal fetal growth as determined by graphic analysis and emperical formulae. Am J Anat, 35: 455.

58. Naquib A, Samman MD, Pamela N, Schultz RN, BS Dennis, A Johnston, Robert W Creasy and Bernard Gonik : Growth hormone like activity levels compared in premature, small, average birth weight and large infants; :Am J Obstet Gynecol, 1987; 157: 1524-8.
59. Niall MD, Hogam ML, Saucer R et al : Sequences of pituitary and placental lactogenic and growth hormones; evolution from a primordial peptide by gene reduplication. Proc Na⁺ Acad Sci USA, 1971; 68: 886 - 870.
60. Noel GL, Suh HK, Stone JG, Frantz AG : Human prolactin and growth hormone release during surgery and other conditions of stress. J Clin Endocrinol Metab.1972, 35: 840 - 851.
61. Overback D, Rutter WJ, Martial JA et al : Genes for growth hormone, chronic somatomammotropin and growth hormone like gene on chromosome 17 on humans. Science 1980; 209: 289 - 292.
62. Roth J, SM Glick, P Cuatrecasas and CS Hollander, 1967: Acromegaly and other disorders of growth hormone secretion. Ann Internal Med. 66 : 760.

63. Roth J, SM Glick, RS Yaldow and SA Berson Science, 140: 887, 1963.
64. Sack J, DA Fisher and CC Wang : Serum thyrotropin, prolactin and growth hormone levels during the early neonatal period in human infants. J Paediatrics, Vol - 89, No-2: 298 - 300; 1976.
65. Salmon WD Jr, Daughaday WH : A hormonally controlled serum factor which stimulates sulfate incorporation by cartilage in vitro. J Lab Clin Med 1957; 49: 825 - 836.
66. Samuel SC Yen, Olof H Pearson and Stanley Stratman: GH levels in maternal and cord blood. J Clin Endocr, 25: 655, 1965.
67. Schalch DS and ML Parker, 1964 : A sensitive double antibody immunoassay for human growth hormone in plasma. Nature, 203: 1141.
68. Schalch DS, 1967 : The influence of physical stress and exercise on growth hormone and insulin secretion in man. J Lab Clin Med, 69: 256.

69. Sheehan HL, Kovacs K, Neurohypophysis and hypothalamus. In Blood worth JMB, Jr ed. Endocrine pathology. Baltimore: Williams and Wilkins, 1982: 45 - 99.
70. Shute CCD and PR Lewis, 1966 : Cholinergic and mono-aminergic pathways in the hypothalamus. Brit Med Bull, 22: 221.
71. Spencer SA, Hammonds RG, Henzel WJ et al: Rabbit liver growth hormone receptor and serum binding protein purification, characterization and sequence. J Biol Chem, 1988; 263: 7862 - 7867.
72. Stubbe P and Wolf H: The effect of stress on growth hormone, glucose and glycerol levels in newborn infants. Hormone metabolism Research 3: 175-179, 1971.
73. Turner RC, B Schnecloch and P Paterson 1971: Changes in plasma growth hormone and insulin of the human fetus following hysterotomy. Acta Endocrinol, 66: 577.
74. Weil-malherbe H, 1960: The passage of catecholamines through the blood brain barrier. Adrenergic mechanisms. CIBA, Foundation symposium JR Vane. GE W Wolstenholme and M O' Conner editors. Little Brown and Co, Boston, 421.

75. William G, Blackard and Sylvia A: Heidingsfelder, 1968 : The J Clin Invest, 47 : 1407-1414.
76. William G, Blackard and Sylvia A: Heindingsfelder; Adrenergic receptor control mechanism for Growth Hormone Secretion, Clin Res, 16: 74, 1968.
77. William H. Daughaday : The anterior pituitary. William Text book of Endocrinology, VIIth Edition, 1985.
78. Yamashita S, Melmed S : Insulin like growth factor-I action on rat anterior pituitary cells: suppression of growth hormone secretion and messenger ribonucleic acids levels. Endocrinology, 1986, 118: 176 -182.
79. Zapf J, Froesch ER: Insulin like growth factors somatomedins: structure, secretion, biological actions and physiological role. Hormone Res, 1986; 24: 121- 30.
80. Delbert A Fisher : Endocrinology of fetal development. In : Jean D Wilson, Daniel W. Foster et al, ed. William's textbook of Endocrinology, 9th Edition. Philadelphia : WB Saunders, 1998 : 1273 – 1301.

81. GD Lakshman Rajesh, B. Vishnu Bhat : Growth hormone levels in relation to birth weight and gestational age. The Indian Journal of Pediatrics. 2000; 67 (3): 175 - 177.
82. Maternal and fetal physiology. Daniel R Mishell, JR Arthur L Herbst. In : Year Book of Obstetrics and Gynaecology, 1998; Mosby: 3 – 8.
83. Maternal and fetal physiology. Daniel R Mishell, JR Arthur L Herbst. In : Year Book of Obstetrics and Gynaecology, 1996; Mosby: 9 – 21.
84. Michael O Thorner, Mary Lee Vance et al : The anterior pituitary. In : Jean D Wilson, Daniel W. Foster et al, ed. William's textbook of Endocrinology, 9th Edition. Philadelphia : WB Saunders, 1998 : 249 – 341.
85. Phillip L Ballard. Hormonal influences on fetal development : In : H. William Taeusch, Roberta A Ballard, Ed. Avery's Disease of the newborn, 7th edition, WB Saunders 1998, pg 32 – 44.
86. John S Parks: Hormones of the hypothalamus and pituitary : In ; Richard E. Behrman, Robert M. Kliegman et al, ed.

Nelson Text book of Pediatrics, 17th edition, Saunders, 2004;

pp 1845 – 47.

87. G.D. Lakshman Rajesh, B. Vishnu Bhat et al: Growth hormone levels in relation to birth weight and gestational age. The Indian Journal of Pediatrics. 2000; 67(3): 175 – 177.
88. I.K. Asthan, J Zapf et al. Insulin like growth factor 1 and 2 in human fetal plasma and relationship to gestational age and fetal size during mid pregnancy. In Daniel R Mishell, Thomas H. Kirschbaum, ed. Year book of Obstetrics and Gynaecology, 1987. Inc.

Working Proforma

WORKING PROFORMA

**Topic: GROWTH HORMONE LEVELS IN NEWBORNS IN RELATION TO
GESTATIONAL AGE AND ANTHROPOMETRIC INDICES**

Thesis Guide: Dr. (Mrs.) Sheela Longia (M.D.)

Case No: Caste:

Name: Age of mother:

Age: Sex :

Date of Birth: MRD No. :

S/o /D/o: MOIC:

Address:

Previous obstetrical History

G P A L

History of recurrent abortion or still birth

Gestational maturity of previous baby

Birth weight of previous baby

Congenital malformation in previous baby

Mode of delivery in previous baby

Pre pregnancy Health status of mother

Hypertension Diabetes

Cardiac failure CRF

Bronchial asthma Thyrotoxicosis

Anaemia Myxedema

Nutrition Hyperparathyroidism

Weight of mother

Stature of mother

Course of pregnancy

Booked / Unbooked

1st Trimester

Blood group of mother

H/O maternal rubella, cytomegalovirus infection

Toxoplasmosis (liver, rash, post cervical lymphadenopathy)

H/O maternal medication

VDRL

HIV, Hepatitis B and TORCH screening

Antenatal visit

Radiation exposure

IInd Trimester

Dietary intake

Weight gain

PIH

Bleeding PV (placenta previa, abruptio placentae)

Oligo hydramnios

Poly hydramnios

IIIrd Trimester

H/O Amnionitis (peripartal fever, Abdominal tenderness)

Prolonged rupture of membrane

Unclean and too many vaginal examination

Labour Prolonged labour

Spontaneous / Induced

Fetal distress during labour

Cephalopelvic disproportion

Cord around the neck / cord prolapse

Analgesics and Anaesthetics during labour

Method of delivery - Vaginal/ LSCS [Elective / Emergency]

Instrumentation

Neonatal History

- Date and time of birth
- Place of birth
- Apgar score at 1 min after birth
- Kept in nursery / Roomed in with mother
- Passage of first urine and stool

Examination

- Gestational age
- LMP
- New Ballard Scoring
- LGA / SGA / AGA

General appearance

Color	Cry		
Activity [Alert / Lethargic / Jitteriness]			
Skull [caput / Cephalhematoma / Fontanelle]			
Hair color		Hair line	
Face	[Eye	Nose	Ear]
Neck		Chest	
Abdomen		Limbs	

Anthropometric examination

Weight	Length
Head circumference	Chest circumference

Systemic examination

Cardio vascular system

Heart rate	Murmurs
------------	---------

Respiratory system

RR	Regular / periodic / apnic attacks
Chest B/L - Clear / sign	

Abdominal examination

Liver size	Spleen - palpable / not palpable
Kidney - palpable / not palpable	Any congenital anomaly